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Is Apixaban (Eliquis®) an Option for Your Patient?

Indications[1]

- ❑ Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
- ❑ Acute VTE treatment & prevention of recurrent VTE [for deep vein thrombosis (DVT) and pulmonary embolism (PE)]**
- ❑ Prevention of venous thromboembolic events (VTE) in elective total hip or knee replacement surgery (THR, TKR)

*CCS definition: AF without mechanical heart valves or without moderate/severe mitral stenosis (rheumatic and non-rheumatic)[2]

**Cancer associated VTE (not an official indication) – data shows similar efficacy and bleeding to LMWH[3,4]

Requirements[1] - NOTE: Apixaban accumulates in hepatic and/or renal dysfunction

- ❑ Stable creatinine clearance (CrCl) greater than 15 mL/min (see dosing recommendations)
- ❑ Stable liver function [refer to Contraindications and Limitations sections below]

Contraindications[1,2]

- ❑ Mechanical heart valves
- ❑ Apixaban, like other anticoagulants, is contraindicated in patients at high risk for bleeding
- ❑ Pregnant/Breastfeeding: Safety & dosing has not been studied. Use is NOT recommended
- ❑ Moderate to severe hepatic impairment associated with coagulopathy and clinically relevant bleeding risk. Patients with severe hepatic impairment or active hepatobiliary disease have not been studied.
- ❑ Drug Interactions: Significant drug interactions involving of both CYP 3A4 and P-glycoprotein - See below

Potential Limitations[1]

- ❑ Not recommended in hemodynamically unstable acute PE or those requiring thrombectomy or thrombolysis
- ❑ Not recommended in antiphospholipid syndrome with a history of thrombosis (especially triple positive)
- ❑ Drug Interactions: AVOID rifampin, select azole antifungals (e.g. ketoconazole, itraconazole but *excluding* fluconazole), select anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital), HIV protease inhibitors, St. John's Wort & other strong CYP 3A4/P-gp inducers and inhibitors as there is minimal knowledge of clinical outcomes
- ❑ Rapid decline in anticoagulant effect after a missed dose; adherence is critical
- ❑ Limited data supporting the use in extremes of weight (under 50 kg; over 120 kg or BMI > 40)[5]
- ❑ Less than 18 years of age: Safety & dosing has not been established
- ❑ Patients with ALT & AST greater than 2x ULN or total bilirubin greater than 1.5x ULN were excluded in clinical trials

May offer an advantage over warfarin if:

- ❑ Difficulty stabilizing on warfarin for reasons other than poor medication adherence
- ❑ INR monitoring is problematic (e.g. poor venous access, frequent travel, remote location).
- ❑ AF: Superior reduction in rate of all-cause stroke and systemic embolism, lower rate of major bleeding, clinically relevant minor bleeding and hemorrhagic stroke compared to warfarin[6]

Dosing Recommendations[1]*

Stroke Prevention in Non-Valvular Atrial Fibrillation**	5mg bid, ***or*** 2.5mg bid if TWO or more of: • Scr 133 µmol/L or greater • 80 years or older • 60kg or less	**CrCl Less than 25 mL/min:** 15-24 mL/min: use caution. (No dosing recommendation) < 15mL/min: Avoid Use
Acute DVT/PE Treatment	10 mg bid for 7 days, followed by 5 mg bid After at least 6 months of treatment, recommended dose for continued prevention of recurrent DVT/PE is 2.5mg BID	**CrCl Less than 30 mL/min:** 15-29 mL/min - Usual dose, but use caution as higher bleeding risk. < 15 mL/min: Avoid Use
Hip & Knee Replacement	2.5 mg bid x 10-14 days (TKR); x 32-38 days (THR)	

* Oral use: May crush & mix with applesauce or suspend in 30mL water. NG tube: May crush and suspend in 60mL D5W.[1,7]

** Apixaban for atrial fibrillation may be used at usual doses in combination with P2Y12 inhibitor (clopidogrel) after ACS or PCI.[8]

 Collaborative Learning on Thrombosis (CLOT) – Canadian Prairie pharmacists with an interest in thromboembolic disorders

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Monitoring Patients on Apixaban

- CrCl should be determined at baseline and at least annually. Monitor more frequently if older than 75y, with renal dysfunction (CrCl <60 mL/min), or when a decline in renal function suspected
- Monitor for symptoms and signs of bleeding
- No routine coagulation testing required. NOTE: INR is not useful for monitoring. Do not target INR 2 to 3. More specialized testing should only be considered in consultation with an expert in anticoagulation.

Switching Between Agents [1]

From warfarin to apixaban:

- Discontinue warfarin and start apixaban once INR is less than 2

From non-warfarin anticoagulant (oral or parenteral - e.g. LMWH, rivaroxaban, dabigatran, edoxaban) **to apixaban:**

- Start apixaban at the time the next scheduled dose of the non-warfarin anticoagulant was to be administered
- For prophylactic dosing of parenteral anticoagulants, apixaban can be started 6 or more hours after the last dose
- For agents administered by continuous infusion, stop the infusion and start apixaban at the same time

From apixaban to warfarin:

- Start warfarin and only discontinue apixaban once INR is 2 or greater. **NOTE:** Apixaban may affect INR; therefore when starting warfarin, INR may initially be unreliable. If possible, checking INR just prior to next apixaban dose may better reflect the anticoagulant effect of warfarin.

From apixaban to non-warfarin anticoagulants (oral or parenteral): (e.g. LMWH, rivaroxaban, edoxaban, dabigatran)

- Discontinue apixaban and give the 1st dose of non-warfarin anticoagulant at the time the next dose of apixaban is due

Management of Bleeding Episodes with Apixaban

- Vitamin K, protamine, tranexamic acid, plasma and/or idarucizumab will not reverse drug effects
- In the event of major hemorrhagic complications, discontinue apixaban and refer patient for urgent assessment and locally developed management strategies
- Limited evidence demonstrates prothrombin complex concentrates (e.g. Octaplex®/Beriplex®) are able to reverse the anticoagulant effect[9], but the effect of these agents on bleeding outcomes is limited.
- Specific antidotes are not yet available in Canada[10]

Anticoagulation around Invasive Procedures [11] (e.g. surgery, elective day procedures, major dental procedures)

- As with warfarin, very low risk bleed procedures (such as dental extraction) do not require withholding apixaban
- Management plans should be made in consultation with the provider performing the procedure
- Renal and hepatic function significantly impacts clearance of apixaban. If the recommendations below cannot be met, consultation with an expert in anticoagulation management is encouraged.
- Due to the onset/offset time of apixiban, peri-procedural use of LMWH is not required

***Pre*-Procedure - If required, stop apixaban before procedure as follows:**

Renal function# (CrCl mL/min)	Last intake of drug prior to procedure	
	Low Bleeding Risk	High Bleeding Risk*
30 or more	at least 24 hours	at least 48 hours
15 - 29	at least 36 hours	at least 48 hours

Limited clinical data for CrCL less than 25mL/min, however, if less than 15mL/min, longer duration likely necessary

* Make a careful decision (i.e. hold longer) for patients undergoing major surgery, spinal puncture, or other regional anaesthesia in whom complete hemostasis required. Consult specialist in these high risk patients/procedures.

For an interactive perioperative management algorithm, see Thrombosis Canada website:
http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm

***Post* Procedure:** Resumption should not be initiated until adequate hemostasis has been achieved and clinical situation allows (usually 1 -3 days). NOTE: Full therapeutic effect occurs approximately 2 hours after ingestion.

References:

1. Eliquis Product Monograph (Pfizer Canada Inc. Bristol-Myers Squibb Canada), October 7, 2019. **2.** Andrade JG et al. Can J Cardiol 2020; 36: 1847-1948. **3.** Agnelli G et al. N Engl J Med 2020;382:1599-1607. **4.** Carrier M et al. Curr Oncol 2018; 25(5):329-337. **5.** Direct oral Anticoagulants in Obese Patients. Thrombosis Canada Website: https://thrombosiscanada.ca/wp-content/uploads/2020/06/DOACS-in-Obesity_24June2020.pdf. Accessed March 15, 2021. **6.** Granger et al. N Engl J Med 2011; 365 (11):981-92. **7.** Song Y, Wang X, Perlstein I et al. Clinical Therapeutics 2015; 37(8):1703-1712. **8.** Lopes RD et al. N Engl J Med 2019; 380:1509-24. **9**. Eerenberg ES, et al. Circulation 2011; 124(14):1573-9. **10.** Connolly S, et al. N Engl J Med 2016;375:1131-1141. **11.** Steffel J, et al. Eur Heart J 2018; 39:1 330-1393.